THE MEDICAL ASPECTS OF ENDOGENOUS UVEITIS

THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF MEDICINE

By

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INTRODUCTION

In 1953 an investigation into the medical aspects of uveitis was undertaken at the request of Professor G. I. Scott of the Department of Ophthalmology of the University of Edinburgh and this thesis embodies the findings in 121 of the patients who attended that department. At the outset it was decided that all patients should have a comprehensive general medical examination with the inclusion of radiography and some laboratory tests, but as the investigation proceeded the probable importance of focal sepsis became apparent and bacteriological tests were added. The results obtained from this study are interesting and encouraging, although it will be some time before their final significance can be assessed.

Inflammation of the uveal tract is one of the major causes of impaired vision and even of total blindness. Ophthalmologists are often unable to arrest the inflammatory process and they can never guarantee a cure. During the last forty-five years several different approaches have been used to attack various aspects of the problem. However, there seems to be general agreement that uveitis is not merely a pathological response of the eye alone but that it probably reflects a reaction of the body as a whole. Consequently during this century the condition has been investigated by

ophthalmologists acting in close co-operation with specialists in other branches of medicine. The results of this co-operation have often been conflicting and have shown remarkable national differences as well as the changes of emphasis to be expected over a period when medical fashion and thought have so profoundly changed.

REVIEW OF THE LITERATURE

By 1910 the view that iritis was predominantly due to venereal disease was being considerably challenged. Butler in 1911 refers to an article by Campbell published during the previous year in which it was said that 70% of cases of uveitis were syphilitic and 20% were due to gonorrhoea, and at the same time the existence of a "rheumatic" uveitis was questioned. Stimulated by the controversy which arose as a result of this article Butler, who had the reputation of being a good and thoughtful ophthalmologist, went through his own personal records of 5,710 patients and found 100 suffering from uveitis. Though he admits his number is small, and his facilities were by present day standards very limited, his clinical approach to the problem was very similar to that in common use today, though there are now in addition a whole series of routine special investigations. Discussing a table showing his results (Table 1) he pointed out that even if all his doubtful cases were actually syphilitic, they would not reach the figure of 70%. The introduction of the Wassermann reaction, at a future date, was to prove him correct on this point at least.

In 1913 Lang published a paper on the "Influence of chronic sepsis upon eye disease" stressing in particular the importance of oral sepsis, but he did not make a clear distinction between sepsis as an associated finding and as an

TABLE I

(after Butler, 1911)

Aetiology	No.	Male	Female
Doubtful	41	16	25
Syphilis	22	9	13
Sepsis Oral Nasal	12	7	5
Gonococcal	6	6	-
Rheumatic	6	5	1
Tuberculosis	6	3	3
Intestinal stasis	4	1	3
Albuminuria	2	-	2
Diabetic	1	1	-
Total	100	48	52

aetiological factor, and consequently he allowed himself to draw conclusions which were unjustifiably sweeping.

By 1914 Rosenow's work was becoming known and accepted and his theory of the aetiology of rheumatism attributing prime importance to the Streptococcus viridans was published that year. About one year later he followed this with a paper on the experimental production of iritis and other ocular lesions in rabbits following intravenous injection of streptococci. His theory of the elective affinity of different strains of organisms for certain tissues became widely accepted, particularly in the United States, and there followed a long period when septic foci were rigorously hunted and ruthlessly eradicated. At first this sacrifice of teeth, tonsils and the pursuit of other eradicating procedures was regarded as a most valuable form of treatment and the literature of the period is filled with reports of successes attributed to them. Most of these reports, however, were very uncritical in their facile acceptance of a causal relationship between focal sepsis and uveitis, a relationship which has never been proved or disproved.

After some years follow-up reports began to appear and in 1926 Irons and Brown published a follow-up of 50 cases after a period of 3-12 years. In this series 23 of the patients had had prior attacks of iritis and 40 were classified as having an iritis caused by septic foci. In 33 patients the focus was eradicated and there had been no relapse; in the remaining 7 cases the focus had not been completely eradicated and there

were two relapses. This paper by Irons and Brown dealt with a group of people who had been carefully and critically examined and is probably an accurate report in contrast with many others which showed little discrimination between fact and fancy.

Since the initial report by Rosenow there has been a steady flow of experimental work on animals. The validity of extrapolating the results of animal experiments to human pathology is always doubtful, not least in relation to ophthalmological problems. In 1930 and 1931 David and Beatrice Seegal published a series of reports referring to the problem of tissue hypersensitivity in general with particular reference to ocular reactions. They based their work on the accepted theories of Koch (1891) and Calmette (1908) and referred to what they called an "ocular anaphylaxis". In a later report of their study of anaphylactic reactions in albino rabbits they drew the following conclusions:-

1) "A sensitised eye reacts to an intravenous injection of homologous antigen 8 months after the sensitising intraocular injection of antigen".

2) "If this intravenous injection of antigen is repeated daily the sensitised eye will finally become desensitised".

From these results, which have been confirmed by other workers (Foss 1949, Benedict 1920 and Lewis 1950) a broader concept of the part played by focal sepsis has emerged. It has been suggested that, for a reason not yet understood and

which at times may be attributed to trauma, one or both eyes can become hypersensitive to bacteria which from time to time enter the systemic circulation in small amounts. The source of the bacteria may be either a localised focus of infection or a mucous membrane or cutaneous surface. In the 1930's this theory of repeated transient bacteraemia and what might be called "target sensitivity" was exhaustively investigated. Although the work of Swift was probably earlier than that of Seegal there followed a series of papers from Swift, MacLean and Derick which agreed in general principle with the work of Seegal. (Derick and Swift, 1929; Swift and Derick, 1929; McEwan and Swift, 1935; MacLean, 1936) MacLean in particular showed that the uveal tract participates in the general sensitisation of the body to the streptococcus and especially to the Streptococcus viridans.

In 1934 Traut, using Clowson's technique of studying streptococci in peripheral blood, recorded 5 positive cultures of peripheral blood taken from patients with uveitis. He said that "these resembled the cultures taken from patients with arthritis". His report however is quite inconclusive and does not seem to have been confirmed independently although it is often quoted subsequently in the literature. In collaboration with other workers, Berens (1934) described a series of careful experiments dealing with the possible consequences to the eye of focal and particularly dental sepsis. He was able to demonstrate a high agglutinin titre to an autogenous strain of

streptococci but he did not stress this finding and merely remarked that it was highly suggestive of the probable importance of the role played by the streptococci. In a further series of experiments on rabbits reported in 1936 he showed that an iritis could be produced in rabbits by the intravenous injection of crude and purified cultures of bacteria isolated from patients with certain inflammatory eye diseases, and he went on to conclude that "iritis is produced in rabbits' eyes by various cultures of bacteria but this property is not characteristic of any one bacterial genus neither is it distinctly a property of cultures from patients with inflammatory eye diseases". In a later series of experiments, reported in 1938, he showed that acute and chronic lesions could be produced in the eyes of rabbits by the intravenous injection of many organisms including haemolytic streptococci, Staphylococcus aureus, Bacterium typhosis, Bacterium coli, Bacillus proteus and Brucella abortus. Furthermore he showed that the uvea was more often affected by streptococci than any other organism and finally that multiple injections were more effective in producing this target response than was a single injection. In 1940 Siniscal was unable to produce an experimental iritis but suggested that over a period of time the uvea could become sensitised to bacteria or their toxins and that at some time the eye could become hypersensitive or allergic to this discharge, subsequently developing an iritis or iridocyclitis.

In any review of the literature on uveitis an important place must be given to the work of Woods and his associates at Baltimore. In 1941 Woods reviewed 562 cases of uveitis in patients who were admitted to the Wards of the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital between 1925 and 1939 (Guyton and Woods, 1941). The latter date was not arbitrarily chosen but marks the time when the possible aetiological significance of sarcoidosis and brucellosis was recognised and the methods of investigation were consequently changed.

He pointed out that during this 14 year period 1,500 cases of uveitis were admitted to hospital for investigation and treatment but because of various shortcomings in their investigation or documentation only 562 could stand statistical analysis. Table II shows what he considers to be the aetiological factors in his series. It will be noticed that he divides his cases into two groups: Group I where there is "definite" evidence of an aetiological factor and Group II where this evidence is only "presumptive". Although he lays down fairly rigid criteria for his differentiation between the two groups this classification is very arbitrary because no causal relationship between non-granulomatous uveitis and syphilis, tuberculosis, gonorrhoea, or other associated conditions has ever been conclusively proven. Though he himself seems fully to realise that even his "definite" diagnosis is really only a presumptive one it has had the effect of giving his discussion of the aetiology of uveitis a

TABLE II
(after Guyton and Woods, 1941)

Aetiologic Factor: Diagnosis, either Definite or Presumptive, for 562 patients with uveitis. (All percentages based on entire series of 562 patients)

	Group I 244 Patients with Definite Evidence of Aetiologic Factor		Group II 318 Patients with Presumptive Evidence of Aetiologic Factor		Total 562 Patients	
Aetiologic factor	No. of Patients	Per-centage	No. of Patients	Per-centage	No. of Patients	Per-centage
Tuberculosis	132	23.5	147	26.1	279	49.7
Syphilis	45	8.0	14	2.5	59	10.5
Sarcoidosis	3	0.5	0	0.0	3	0.5
Brucellosis	1	0.2	1	0.2	2	0.4
Foci of infection	31	5.5	116	20.6	147	26.1
Gonorrhoea	10	1.8	16	2.8	26	4.6
Non-granulomatous systemic disease	14	2.5	19	3.4	33	5.9
Metabolic disease	0	0.0	3	0.5	3	0.5
Miscellaneous	8	1.4	2	0.4	10	1.8
Total	244	43.4	318	56.5	562	100.0

spurious authenticity. The fluidity of ideas is well shown by Woods in a later paper published in 1944 when he added a further 200 cases to the previously reported 562. During the intervening years the incidence and possible importance of sarcoidosis and brucellosis had been appreciated and patients were consequently investigated with these possibilities in view. This resulted not only in the inclusion of a new group of so-called aetiological factors but also in a striking decrease in the importance given to focal infection (Table III).

The presumption of the probable importance of the "granulomatous" diseases (syphilis, tuberculosis, leprosy, sarcoidosis, brucellosis, histoplasmosis, toxoplasmosis) led Woods to divide his cases of uveitis into two large groups: those due to granulomatous and those due to non-granulomatous disease. This classification was made by a clinical examination of the eye when the patient was first seen and though not rigid or applicable to all cases Woods maintains that the majority of early cases at least may be classified into one or other of these groups. Though this classification is not accepted by many ophthalmologists it is interesting that two of the leading ophthalmologists of Belgium and France, Morax (1950) and Francois (1950), accept this classification and tend to minimise, almost to the point of exclusion, the importance of focal sepsis as a possible cause of non-granulomatous uveitis. Instead they prefer to classify the

Table III
(after Woods and Guyton, 1944)

Aetiologic Factors of Uveitis, either Definite or Presumptive, in Present Series of Two Hundred Patients

Aetiologic Factor	Group I 102 Patients with Definite Evidence of Aetiologic Factor		Group II 98 Patients with Presumptive Evidence of Aetiologic Factor		Total 200 Patients	
	No. of Patients	Percentage [x]	No. of Patients	Percentage [x]	No. of Patients	Percentage
Tuberculosis	39	19.5	43	21.5	82	41.0
Syphilis	24	12.0	4	2.0	28	14.0
Sarcoidosis	15	7.5	0	0.0	15	7.5
Brucellosis	0	0.0	15	7.5	15	7.5
Foci of infection	4	2.0	8	4.0	12	6.0
Rheumatoid arthritis	5	2.5	0	0.0	5	2.5
Gonorrhoea	7	3.5	6	3.0	13	6.5
Miscellaneous	8	4.0	0	0.0	8	4.0
Undetermined origin [1]	0	0.0	22	11.0	22	11.0
Total	102	51.0	98	49.0	200	100.0

[1] The 22 cases of uveitis of undetermined origin consist of 9 cases of granulomatous uveitis and 13 cases of non-granulomatous uveitis.

[x] Percentages are given on the basis of the total series of 200 cases on which this report is based.

cause as being unknown and in a two year period at the hospital of Lariboisere, Morax examined 252 cases of iridocyclitis of which 168 were classified as being of unknown origin. Furthermore though he gives a very small place to focal sepsis his idea of it is not that currently held by Woods and other American workers. He admitted that perhaps 7% of his cases had a dental focus of sepsis but he emphasised that this focus of dental sepsis was almost always on the same side as the affected eye, and did not accept the theory of bacterial hypersensitivity to which the Americans and other workers are now giving considerable stress. Also the French workers draw particular attention to their very frequent finding of multiple pathology.

There has been no recent report of a large series of cases from this country but, as so often happens, there appears to be a paucity of extreme opinions and a general acceptance of the traditional British middle road. This is summed up by Duke-Elder (1954) who, while admitting aetiological ignorance and therapeutic impotence, advises a general medical examination with particular reference to tuberculosis, gonorrhoea, syphilis and focal sepsis. If any of these conditions is discovered it should be dealt with in a conventional manner but the approach is conservative and no radical measures should be embarked upon unless they can be completely justified. Finally, he lays particular stress upon the general reaction of the individual and emphasises the very close relationship between "the seed and the soil".

Focal Sepsis

Although some of the theories which link iridocyclitis and focal sepsis have already been mentioned, a more detailed discussion of the subject is demanded by reason of the mass of literature to which these theories have given rise. Moreover it is interesting to trace the modifications and changes of emphasis to which these hypotheses have been subjected and also to note that, though they have not been fully vindicated, they have never been conclusively discredited.

Reference is made in the literature of the 19th. century to the importance of septic foci as a possible causal factor of systemic disease but Hunter (1901) is widely regarded as the originator of the theory which attributes to dental sepsis a role of major importance. Nevertheless it was not until 1916 that the wide publicity that Billings gave to the theory resulted in it gaining many adherents and the experimental work of Rosenow (1914, 1915) supported by the clinical reports of Lang (1913), Benedict (1920) and others brought about a wide acceptance of Hunter's views.

The primary focus of sepsis may be dental, tonsillar, respiratory, alimentary, genito-urinary, or in any part of the body which is able to harbour organisms and allow them access from time to time into the circulation, thereby making possible the occurrence of reactions at a distance from the primary focus.

The evidence which has been produced in favour of the

importance of focal sepsis would appear to be:

1) Septic foci are often found during the routine systemic examination of patients.

2) Transient bacteraemia has been detected during the course of various diseases such as sub-acute bacterial endocarditis and following such procedures as dental extraction (Okell and Elliott, 1935; Siniscal, 1940; Matthew,1950; Coffin and Thompson, 1956). It is also a fact of clinical experience that some patients have an exacerbation of arthritis or iritis after radical surgery or manipulation of an infected site.

3) Some bacteria seem to show a degree of tropism or elective affinity for the uveal tract (Rosenow).

4) Eradication of septic foci has often been followed by clinical improvement.

The plausibility of the theory reinforced by the sense of frustration which has been felt by ophthalmologists confronted with patients suffering from uveitis accounts for the energetic campaign which has been waged against septic foci, real or supposed, since the beginning of the century. The careful work of Irons and Brown (1926) did much to give support to this practice but it soon became clear that the relationship between a septic focus and a "secondary" target was more complex than had first been thought. In 1928 Holman, in 1929 Swift and Derick and later the Seegals in 1930 as well as many others, showed clearly that tissue

hypersensitivity or allergy played a very important intermediary part in these reactions and this was supported by a series of convincing animal experiments by these and other workers. This was followed by a series of reports from Berens and MacLean, working separately, on the importance of tissue sensitisation and the potency of the streptococci in producing sensitivity. At about the same time there were reports by Okell and Elliott (1935) on the occurrence of a transient bacteraemia during dental extraction when as high a proportion as 75% of their patients showed streptococcal bacteraemia following removal of infected teeth. While focal sepsis was enjoying this popularity there were, however, many opponents who disagreed not only on theoretical but on experimental grounds. Furthermore there were some of its most ardent early supporters such as Cecil and Angevine (1938) who showed by their follow up studies that in many cases the eradication of septic foci was apparently of no value. Reiman and Havens (1940) also, while agreeing that obviously septic foci such as badly infected teeth or tonsils should always be removed, opposed the general principles of the theory. Woods, however, in all his publications, though he may have changed the emphasis, concedes that focal sepsis plays an important part in the production of uveitis and refused to discard the theory to which specialists in other branches of medicine have no longer been able to subscribe. Thus, though in the years just before and during the last war, he was most loth to

diagnose uveitis as being probably due to a septic focus and preferred if possible to incriminate what he terms a granulomatous disease, he has now tended to return to his earlier belief in the importance of focal sepsis and bacterial hypersensitivity. In 1950 and again in 1953 Woods published papers on the importance of streptococci in the production of what he terms non-granulomatous uveitis. After recapitulating the hypotheses on focal sepsis and bacterial hypersensitivity in the aetiology of uveitis he comments once again on the association between the rheumatic conditions, uveitis and streptococcal infection and refers to the controversial significance of a raised antistreptolysin titre in uveitis demonstrated by Schöne and Steen in 1947. The reasoning for this more recent concept may be summarised as follows:

If non-granulomatous uveitis is the result of an allergic reaction due to hypersensitivity of the uveal tract to certain streptococcal toxins the following criteria should be satisfied.

1) High incidence of infective foci harbouring streptococci.
2) Lower incidence of granulomatous disease in this group.
3) High incidence of streptococcal sensitivity.
4) The cutting short of the attack of uveitis and the prevention of recurrences by specific desensitisation.

In order to discover whether or not bacterial hypersensitivity was present Woods carried out skin tests with a group of stock streptococcal vaccines and with some autogenous

vaccines recovered from the patients themselves. These tests were performed on 208 patients who had previously been divided into the two categories, granulomatous or non-granulomatous uveitis. The results are summarised in Table IV.

It is interesting that he found foci of infection in 55% of the non-granulomatous group as compared with 28% of the granulomatous group. The latter figure compares closely with his figure of 29% of focal sepsis in his earlier survey of 562 cases, when the sharp differentiation between the two types of uveitis was not made. A further point of interest is that positive evidence of granulomatous disease was found in only 9.8% of the cases classified on ophthalmological grounds as suffering from a non-granulomatous uveitis.

Having made these observations and concluded that in this group the uveitis was due to hypersensitivity to certain organisms he embarked on desensitising the patients. Because of the real danger of inducing high cutaneous sensitivity and low serum precipitin and agglutinin titres, as shown by Derick and Swift and others, all desensitisation was carried out intravenously. The initial dose was 0.1 ml. or 1/100 dilution of the final T50 dilution and the dose increased until 0.5 ml. of T50 dilution was being given. When cutaneous reactivity was abolished a weekly maintenance dose was continued for several months. Using this technique he claimed that an 80% cure was achieved there being no relapses in 5 patients after 8 years and in 22 patients for a period between

TABLE IV

Incidence of Bacterial Hypersensitivity in Patients with Non-granulomatous and Granulomatous Uveitis (Woods,1953).

Type of Uveitis	No. of Patients	Specific Bacterial Hypersensitivity				Total Positive Reactions	Total Negative Reactions
		Stock Streptococcus Vaccines	Stock and Autogenous Streptococcus Vaccines	Autogenous Streptococcus Vaccines only	Other Organisms		
Nongranulomatous	101	73	8	7	2	90, or 89%	11, or 11%
Granulomatous	107	21	0	0	0	21, or 20%	86, or 80%

10 months and 2 years.

Much work remains to be done even in this rather restricted group of cases but from this brief review of focal sepsis it would seem that the wheel has turned full circle and though it may now be pneumatic instead of iron shod the concept of focal sepsis associated with the more recent views on bacterial hypersensitivity may prove to be an elucidation of at least part of the complicated puzzle of uveitis.

MATERIAL AND METHODS

During the two year period of this investigation 149 patients with uveitis were seen by Professor Scott at the Department of Ophthalmology where they were classified into the following groups:

Type I - Non-granulomatous

Type II - Those with mutton fat KP but with no nodules on the iris and no foci of choroiditis.

Type III - Granulomatous

The patients were then referred to the Department of Radiology where routinely the following X-ray photographs were taken:

1. Chest
2. Sinuses
3. Teeth (if edentulous, occlusal maxillary and half mandible films were taken).
4. Sacro-iliac joints.

They were then given an appointment for their comprehensive medical examination.

In an investigation such as this where the full significance of all the findings may be appreciated only in retrospect, it is most important that all the patients should, in so far as is possible, be submitted to the same type of examination and the findings resulting from this should be classified in such a way that they can be marshalled at the

end of the investigation. Consequently an examination scheme, which was slightly modified from that in current use at the Wilmer Institute of Ophthalmology, Baltimore and originally devised by Woods, was adopted. This consisted of:

1. Full medical history, particular attention being given to any possible precipitating factors associated with the initial attack and subsequent relapses. Also an attempt was made to assess the patient's general reaction to his condition so as to try to ascertain any possible associated psychological factors.

2. General physical examination.

3. Examination of urine for protein and sugar.

4. Haematological examination; routinely, haemoglobin estimation, leucocyte count and erythrocyte sedimentation rate. This was followed by further haematological investigations where they were deemed necessary.

5. Wassermann reaction and gonococcal complement fixation test:

6. Mantoux test.

Particular attention was paid to the patient's teeth and, even in the few cases where these appeared to be in fairly good condition, the x-ray findings were very carefully considered. Patients showing any sign of dental sepsis were referred to the Dental Department where they were seen by Dr. Middleton by special appointment.

At the initial examination:

1. A report was made on the general state of the patient's mouth with a survey of the teeth in it.

2. If present, the type of infection was identified in so far as was possible in the two categories: (a) open and (b) closed.

3. Treatment was then recommended.

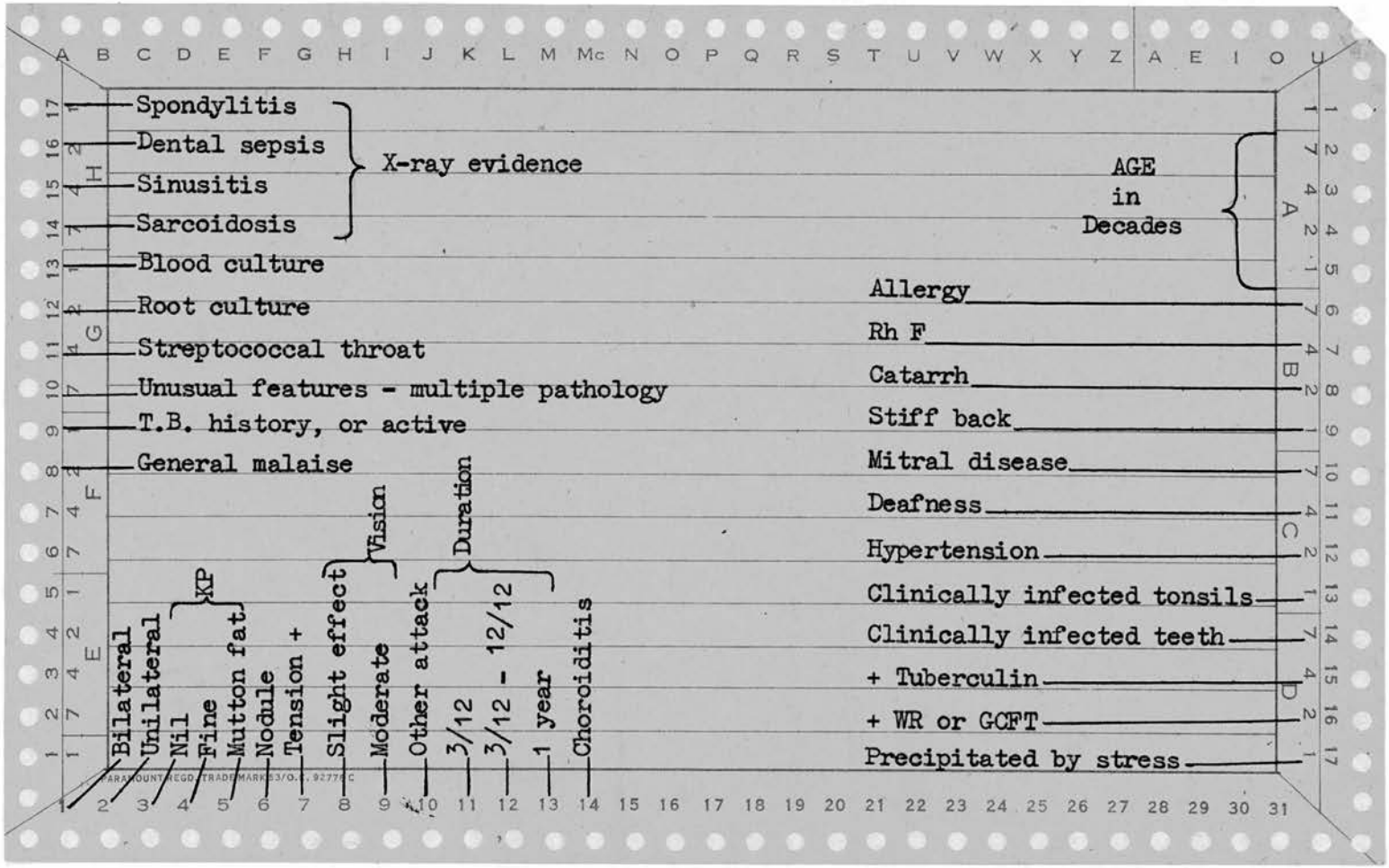
In those patients requiring extraction of teeth an appointment was made for this to be carried out. The extracted tooth, or teeth, were put into sterile containers and sent to the Bacteriology Department where, using aseptic techniques, cultures were taken from the root canal. These cultures were set up in the Bacteriological Laboratory at the Royal Infirmary under the direction of Dr. Bowie and subsequently sub-culture and typing was carried out by Dr. Constable in the University Laboratory.

During the last nine months of the investigation a further routine procedure was added to the dental examination. This consisted of taking samples of venous blood before and after extraction and sending these for culture.

Other foci of sepsis, such as sinuses, tonsils and the urethra were dealt with in the respective special clinics at the Royal Infirmary but it was not thought to be worth while attempting to recover any bacteriological specimens from these sites.

These examinations were generally carried out while the

patient was an out-patient, unless the severity of the uveitis or another associated condition necessitated admission to hospital. In the former case the patients were admitted to the Ophthalmological Wards under the care of Professor Scott while, if the condition meriting admission was a purely medical one, they were admitted to a small research ward in the charge of Professor Dunlop and looked after by myself under his supervision.


Spondylitis
Dental sepsis
Sinusitis
Sarcoidosis
X-ray evidence
Blood culture
Root culture
Streptococcal throat
Unusual features - multiple pathology
T.B. history, or active
General malaise
AGE in Decades
Allergy
Rh F
Catarrh
Stiff back
Mitral disease
Deafness
Hypertension
Clinically infected tonsils
Clinically infected teeth
+ Tuberculin
+ WR or GCFT
Precipitated by stress
Bilateral
Unilateral
Nil
Fine
Mutton fat
Nodule
Tension +
KP
Slight effect
Moderate
Other attack
Vision
3/12
3/12 - 12/12
1 year
Duration
Choroiditis

Case Recording

At the initial medical examination the patient's history was written on a standard 8 x 5" Copeland Chatterson punch card and when all the information about the patient had been collected and assessed the relevant facts were punched on the card according to a master key (see opposite). This method proved to be extremely flexible and made the classification of patients in various groups and categories a comparatively simple and accurate procedure.

Although the number of patients referred for investigation was 149, because of unwillingness on the part of some patients to co-operate, incompleteness of the records and other causes, the records of only 121 patients were found to be suitable for inclusion in the final analysis.

FINDINGS EMERGING FROM THE HISTORY AND GENERAL MEDICAL EXAMINATION

Age and Sex:- The general pattern of the age and sex distribution of the whole series is shown in Table V, while that in the different categories is shown in Tables Va, Vb and Vc. Though there is a clear predominance of females in the whole group the sex incidence will be shown to be closely related to the category of the ocular lesion so that in the largest group, where the lesion is classified as non-granulomatous, the sex difference is not significant. The sex ratio in certain categories, however, with a predominance of females over males is in keeping with a widely held clinical impression that women are more likely than men to develop an iritis. This has tempted some clinicians to postulate a possible endocrine basis as being the responsible factor. Unfortunately, no support for this can be deduced from the findings in the present series and this is not surprising when the crudeness of the means at our disposal of assessing endocrine balance is considered. It is possible clinically to establish only the grosser deviations from normal and it is only in a few endocrine disorders that objective biochemical and other laboratory evidence can be produced in support of a clinical diagnosis. Consequently it can be stated categorically that no simple common factor such as menstrual disturbance or some vague endocrine imbalance could be discovered as a common factor in this series.

TABLE V

ALL CASES - AGE AND SEX DISTRIBUTION

Age	10-19	20-29	30-39	40-49	50-59	60+	Total	Per cent
Male	2	5	12	17	11	2	49	40.5
Female	4	20	13	12	14	9	72	59.5
Total	6	25	25	29	25	11	121	100

TABLE Va

TYPE I - NON-GRANULOMATOUS

Age	10-19	20-29	30-39	40-49	50-59	60+	Total	Per Cent
Male	1	3	11	12	9	1	37	46.2
Female	1	14	7	9	7	5	43	53.8
Total	2	17	18	21	16	6	80	100

TABLE Vb

TYPE II - MUTTON FAT K.P.

Age	10-19	20-29	30-39	40-49	50-59	60+	Total	Per Cent
Male	-	2	-	1	1	-	4	20
Female	1	3	4	1	4	4	17	80
Total	1	5	4	2	5	4	21	100

TABLE Vc

TYPE III - GRANULOMATOUS

Age	10-19	20-29	30-39	40-49	50-59	60+	Total	Per Cent
Male	1	-	1	4	1	1	8	40
Female	2	3	2	2	3	-	12	60
Total	3	3	3	6	4	1	20	100

Rheumatic Diathesis:- A history of rheumatic fever was given by 3 (2.4%) of the patients, though another patient with no history of having had rheumatic fever was found on clinical examination to have well developed mitral disease. Only one of the patients had rheumatoid arthritis which was not active, and in particular no rheumatic history could be elicited from the six patients aged under 20 years, despite the emphasis given to the high incidence of rheumatic disorders in this age group reported by Davis in 1953.

The association of uveitis and rheumatoid arthritis has been accepted since 1910 when Ohm is attributed with the description of the first case in a child of nine years. Though many theories have been put forward the association between the two remains as mysterious as their cause.

In 1939, however, Todd produced some interesting though inconclusive evidence about the raised antistreptolysin titres in rheumatoid arthritis and it is interesting to consider how often the streptococcus has been invoked as a causal factor in these two conditions. Again, in the Milroy Lectures for 1954, Long added considerably to the weight of opinion invoking the haemolytic streptococci and individual allergy to them as being the responsible factors in rheumatic fever. Unfortunately the findings in this series shed no further light on the possible existence of a common aetiology.

Ankylosing Spondylitis:- A striking feature was the very high incidence of ankylosing spondylitis. Ten proven

cases of ankylosing spondylitis occurred in this series giving an incidence of 8.2%; the sex ratio of 8 male cases and 2 female cases falls into the generally accepted range but the overall incidence of the condition is remarkably high and once again suggests the possibility of a common aetiology as the responsible factor for the two conditions.

Despite considerable interest in the condition still surprisingly little is known about ankylosing spondylitis and recent workers (Kellgren et al, 1953; Baird, 1955) have suggested that it has an incidence of about 1 in 1,000 to 2 in 1,000. Iritis is said to occur as a complication in up to 20% of cases and in 1951 Birkbeck reported 11 cases in one year where a diagnosis of ankylosing spondylitis was elicited because of an initial complaint of iritis.

In 1947 Campbell pointed out the high proportion of infective conditions preceding spondylitis and cited gonorrhoea, non-specific urethritis, tuberculosis, tonsillitis and lung abscess. He suggested that it might be an expression of "some local tissue hypersensitivity precipitated by widely differing antigens". There have been reports by West (1949), Tegner and Lloyd (1949) and Mason (1951) on families with at least three proven cases in this country and, in the United States, Hersh (1950) from a study of 50 families concluded that the disease was transmitted by an autosomal dominant gene with a much greater likelihood of its becoming manifest in the male than in the female. A similar theory is not,

however, postulated for the associated iritis. The type of uveitis associated with ankylosing spondylitis is almost always non-granulomatous and in this series 7 of the 8 males and the 2 females were in Category I of non-granulomatous uveitis. Not surprisingly, considerable importance has been attributed to the possibility of a common aetiological factor and especially the incidence of streptococcal sensitivity.

Although it is obviously desirable to treat both pathological conditions when they are found in association, it is unfortunate that until recently the usual symptomatic treatment of rheumatoid arthritis and the radiotherapy of ankylosing spondylitis have had little effect on the iritis. The advent of locally applied cortisone in the treatment of iritis has, however, been particularly beneficial in this group because it can be given without any risk of systemic disturbances while treatment for the other condition is in progress. Thus the severity of an attack of iritis can be diminished and its duration shortened without, unfortunately, preventing any future recurrences.

Hypertension:- The incidence of hypertension in this series was surprisingly high as 12.4% of the patients had diastolic pressures consistently over 100 mm/Hg. No suggestion is made that there is a direct relationship between hypertension and uveitis and it is probably merely another indication of the high morbidity within this group. The following case is described because it shows some interesting features

and may serve to emphasize the high incidence of morbidity in this series.

Mrs. E.G., 21 years, nulliparous, no miscarriages. With no significant history of illness or even ill health and apparently a perfectly healthy young woman, she was found on examination to have a consistently raised blood pressure, the reading being 244/144 mm.Hg. after lying down for a quarter of an hour. Her apex beat was displaced outside the mid-clavicular line but was still in the 5th. intercostal space and no other abnormality was detected. Her urine contained a trace of protein with no casts. She was admitted to Ward 21 and fully investigated. No cause for her hypertension was discovered but in view of its severity she was stabilised on hypotensive drugs and followed up at the Out-Patient Clinic.

The investigation of this case was unrewarding and this unfortunately was a typical feature of the majority of the cases in this series so that it should be emphasised that, unless the actual treatment of their ocular condition warrants it or that a medical condition exists which necessitates admission to hospital, at the present time little is likely to be gained by a more widespread admission of these patients as it disturbs even further their daily life without bringing commensurate benefits.

Findings in the Ear, Nose and Throat

Hearing:- The hearing of 12.4% of the patients was seriously impaired. The incidence of deafness in the population as a whole, as reflected by the use of hearing aids, is about 1% and the total incidence of impaired hearing is probably not more than 3-4%, so that the figure of 12.4% for this series is surprisingly high. The possible importance of deafness was not fully appreciated until the series was almost complete so that unfortunately no further information is available about the cause of deafness. As far as can be judged from their history however, it was due in the majority of cases to middle ear infection early in life.

Sinuses:- It is very difficult to assess the importance of the radiological finding of sinus infection and when considered alone it may be of little significance. This would seem to be borne out by the finding of radiological evidence of sinus infection in this series in 19.8% of the uveitis cases compared to 30% in the control group. Because of the doubt about any advantage that might be gained from special investigation, as well as because of the absence of any symptoms referable to their nasal air passages, few of these patients were referred to an ear, nose and throat specialist.

Throat:- Chronic infection of the tonsils and a history of recurrent sore throats was found in 8.2% of the series; while no figures are readily available for the whole population these figures would appear to be rather high.

Unusual Features

Table VI shows the occurrence of some of the less usual medical conditions which were found in this series. In addition to this 16.3% of the patients associated the onset of the uveitis with a period of unusual stress and 12.1% volunteered that the onset of the uveitis or a recurrent attack was accompanied by a general feeling of malaise. Although no definite conclusions may be drawn from these findings they emphasise that there is a very high incidence of general morbidity in this series of patients and this finding may well have some direct association with the ocular condition.

TABLE VI

Condition	Number
Carotid aneurysm	1
Chronic appendicitis	1
Chronic cystitis	1
Congenital megacolon	1
Diabetes	3
Eunuchoidism	1
Hepatic cirrhosis	1
Obstructing inguinal hernia	1
Periarteritis nodosa	1
Sarcoma of the pelvis	1

Dental Sepsis

The incidence of dental sepsis for the whole series was 40.5% and the relevant figures are shown in Table VII. The higher incidence of dental sepsis in men (49%) compared to women (34.4%) is surprising but unfortunately the numbers involved are not great enough to allow any definite conclusions to be deduced and the same applies to the incidence of dental infection in the different categories of uveitis.

The finding of so high a rate of dental infection in this group of patients is interesting but it is not possible to evaluate its significance because the radiological evidence of dental sepsis in a control group of patients was found to be 34% (see Appendix A). The incidence of radiological evidence of dental sepsis in the control group of patients is surprisingly high and suggests that if a relationship exists between dental sepsis and uveitis it would have to be explained by the response of the patient to the organisms in the focus of sepsis rather than by the mere existence of the focus itself.

Type of Sepsis:- The organisation for recovery and "typing" of the organisms responsible for the dental infection was not in existence from the beginning of the study but after it became so all patients shown by radiography to have dental sepsis were dentally examined and subsequently extraction was arranged. Not unnaturally there was incomplete co-operation from the patients in this matter and this further reduced the number of patients who could be included in the series. Despite

TABLE VII

DENTAL SEPSIS

	Type I		Type II & Type III		All Types	
	Male	Female	Male	Female	Male	Female
Radiological Evidence	19 (56.7%)	11 (25.6%)	5 (41.6%)	13 (44.9%)	24 (49%)	24 (34.4%)
Root Culture	11	5	4	9	15	14
Blood Culture	2	1	3	2	5	3

this, however, the figures are very suggestive. Root culture carried out by the technique already described was positive in 29 cases (59.2%). As was to be expected the responsible organisms were streptococci, and the Streptococcus viridans was isolated from 13 patients. Though typing was carried out in the majority of cases it was not possible to show that a particular type of streptococcus predominated. A summary of the bacteriological findings referring to these investigations which were carried out by Dr. Constable is presented in Appendix B and is included with his permission. The full findings will be published separately at a later date.

Blood Culture:- In seven cases the identical organism isolated from the root canal was cultured from a post-extraction sample of venous blood. In 1949 Matthew and Gilchrist had shown the importance of dental sepsis and bacteraemia in patients with subacute bacterial endocarditis and the occurrence of a transient bacteraemia after dental extraction has been accepted since 1935 when it was described by Okell and Elliott and its importance has recently been stressed once again by Hobson and Jensen (1956). In 1956 Coffin and Thompson showed that the incidence of bacteraemia following dental extraction depended very much on the amount of manipulation of the tooth, the type of roots and the technique employed by the operator.

In the hope of demonstrating a pre-extraction bacteraemia a few patients were given chewing gum to chew for ten minutes

before extraction but no growth from any of these blood cultures was obtained. Despite this, however, it seems reasonable to assume that from time to time the trauma of chewing associated perhaps with some exacerbation or extension of the local infection should result in a bacteraemia.

Focal Sepsis

It should be unnecessary to emphasise the very great difficulty in evaluating the importance of focal sepsis in endogenous uveitis and it seems more likely that it is the individual's response to a septic focus which may determine the evolution of inflammation in the uveal tract rather than the mere presence of a septic focus. There is furthermore the difficulty of trying to decide what exactly constitutes a septic focus but, if the criteria on which this is judged remain constant throughout the series, it would be of considerable interest to see if there is any variation in the incidence of septic foci in the different categories of uveitis, not only in this series but compared to cases reported elsewhere. Consequently for the purposes of this particular study it was decided to accept evidence of focal infection where there was:-

1. Radiological evidence of dental infection
2. Radiological evidence of sinus infection
3. Other sources of focal infection proven bacteriologically, such as tonsillitis.

Table VIII gives the results of this grouping.

The total incidence of sepsis in the two groups is virtually identical and this would seem to suggest that if the presence of a septic focus is responsible for the development of a uveitis it in no way determines whether the uveitis is granulomatous or non-granulomatous and consequently some other factor must be involved. This finding differs very strikingly

TABLE VIII

FOCI OF INFECTION

	Type I Non-Granulomatous	Type II & III Granulomatous
No. of patients	80	41
Teeth	30 (37.5%)	18 (43.9%)
Sinuses	14 (17.5%)	3 (7.3%)
Other	5 (6.2%)	3 (7.3%)
Total %	61.2%	58.5%

from a recent series published by Woods in 1953 (see Table IV) which has been discussed earlier in the review of the literature. The grouping in this series for this particular comparison is identical to that employed by Woods and it appears clear that from these findings no support whatsoever can be given to his contention. Additional evidence against Woods' theory is also provided by the very low incidence of granulomatous disease discovered in the present series.

Nevertheless, acting on the assumption that a majority of the patients with a non-granulomatous uveitis had developed a sensitivity to some endogenous source of infection, Woods carried out specific desensitisation with apparently beneficial results. Consequently, in the absence of any more positive line of attack it would seem desirable to carry out skin tests as described by Woods in those patients who are found to have septic foci and on the results of these to set about specific desensitisation in the hope that not only might the patients be immediately benefited but that some further light might be cast on the aetiological problem of uveitis.

GENERAL MORBIDITY IN THIS SERIES

From the medical examination of this series a general impression was gained that these patients suffering from uveitis had a remarkable incidence of either poor health or actual positive disease. Because so much doubt still exists about the validity of assessing focal sepsis from radiological examination and because of the high rate of focal sepsis found in a control group it would not be generally acceptable to consider the mere presence of focal sepsis as being necessarily indicative of disease. If, however, the radiological evidence of focal sepsis, as well as the presence of tonsillitis and other possible sources of sepsis, is not included as a measure of morbidity and instead criteria are used such as would be followed for a life insurance examination the morbidity rate is still surprisingly high.

Thus, if this series is judged on the standard as to whether or not they would have passed an ordinary general medical examination such as for Life Assurance the surprising number of 46.2% show positive evidence of disease and would be turned down or deferred until some specific treatment had been given. These figures emphasise once again that the "state of the soil" is an important determining factor and may even be one of the prime components necessary for the development of uveitis.

NEGATIVE FINDINGS

No patient in this series gave a history of syphilis, nor was there a single doubtful Wassermann test. Only three patients gave a history of gonorrhoea and they also had positive gonococcal complement fixations tests. The iritis of two of these latter patients was classified as non-granulomatous while the other patient whose uveitis was of a granulomatous type did not show the typical ocular picture of a plastic gonococcal iritis.

A history of tuberculosis was elicited from only two patients and despite exhaustive examination it was shown to be inactive in both. Furthermore, these two patients showed a granulomatous and non-granulomatous type of iritis respectively. The Mantoux test was performed on the great majority of patients but retesting of the negative reactors to low dilutions was not possible for the whole group owing to the difficulty of getting the patients to report back and also to the difficulty of getting an accurate reading of the test done when the patient lived far from hospital. The variability of the positive responses however has not, in this series at least, shown the test to be of any value as a screening procedure though it should be routinely carried out in children and in any cases where sarcoidosis is suspected.

The importance of sarcoidosis as an aetiological factor stressed by Woods was unsupported by the findings in this

series where there was only one proven case and one doubtful one, and may be accounted for in part by the fact that this condition is said to be 17 times more common in negroes (Middleton, 1954). In 1950 Lewis described six cases of sarcoidosis in Australia occurring in a series of 26 patients with choroiditis and he stressed that a typical feature was mutton fat K.P.

No patient gave a history suggestive of brucellosis and though at the beginning of the series agglutination tests for typhoid and cold agglutinins were performed these were found to be of no diagnostic value and very wasteful of laboratory time so that they were not continued routinely and were included only when the history suggested that they might be of some diagnostic help. Apart from the value of the erythrocyte sedimentation rate as an indication of some generalised systemic upset and a raised leucocyte count where definite sepsis was present, haematological investigations proved to be of little diagnostic value although they were included as part of the routine medical investigation. Finally, as it was not possible to carry out any laboratory tests for toxoplasmosis no conclusions about the significance or incidence of this condition as an aetiological factor can be drawn from this series.

These negative findings are very much in accord with those of the recent English series by Smith and Ashton (1955) but contrast strikingly with those of earlier workers. (Table IX) It is clear that the findings of this series are in keeping with

TABLE IX

Authors	No. of Cases of Uveitis	Syphilis %	Tubercu-losis, %	Gonor-rhoea %	Focal Infection %	Rheuma-tism %	Other Causes %	Un-Known %
Butler, 1911 (E)	100	22	6	6	16	6	3	41
Elschnig, 1912 (E)		21	28		19	15.5		15.5
Irons and Brown, 1916 (A)	100	23	8	9	59			1
Irons and Brown, 1923 (A)	100	15		1	75			9
Bulson, 1925 (E)	100	33		5	58		2	2
Elschnig, 1925 (E)	141	20	24.5		37.5	9		21
Newton, 1925 (A)	75	13.3	2.6		35.8		22.6	25.3
Gilbert, 1929 (E)	500	16.6	45.6	3	6.4			17.4
Gifford, 1930 (A)	118	16.9	8.5	6.8	41.5		1.7	32.6
Guyton and Woods, 1944 (A)	762	11.4	47.3	5.1	20.9		11.2	2.8
Paufique and Vincent, 1947 (E)	133	2.2	23.3	1.5	27	0.7		41.3
Morax, 1950 (E)	160	12	18	5.6	7			50

E = Europe A = America

the general trend of a decreasing incidence of venereal disease and tuberculosis, resulting from the epidemiological control of these conditions. Although not in itself constructive this cutting away of the dead wood of outmoded theories is one of the first essentials to a rational approach to this problem from which it is hoped that some positive advance may result.

OCULAR FINDINGS

Although it is outside the scope of this thesis to discuss the ophthalmological aspects in great detail, it is its aim to present some of the ocular findings in such a way as to see if any conclusions regarding aetiology and prognosis may be drawn from them. Unfortunately the number of patients in Types II and III is so small that it is only possible to generalise about Type I or the group as a whole. Any observations made about Type II and III alone could hardly be justified by the small numbers of each, though some tentative remarks may be made about the combination of Types II and III which Woods would classify as one group under his heading of "granulomatous" uveitis.

Table X gives the main ocular findings for the series and from these figures relating to the series as a whole the following general statement may be made. In three-quarters of the cases of uveitis one eye only is involved while vision is seriously affected in only one-third of the cases. In about half the cases the attack lasts less than three months but at least one-third of the patients experience further attacks. When it is remembered that Sorsby (1950) has shown that more than 7.9% of total blindness in this country is due to uveitis these findings take on a deeper significance.

Despite the small numbers the differences in the extent of visual involvement shown by Table X, as well as the tendency to

TABLE X

OCULAR FINDINGS

	All types	Type I		Type II		Type III	
		Non-granulomatous		Mutton fat K.P.		Granulomatous	
		Male	Female	Male	Female	Male	Female
Bilateral	26(21.4%)	4(10.9%)	9(18.9%)	1(25%)	7(41.2%)	-	5(38.4%)
Unilateral	95(78.6%)	33(89.1%)	34(81.1%)	3(75%)	10(58.8%)	7(100%)	8(61.6%)
Raised tension	13(10.7%)	5(13.5%)	2(4.6%)	-	5(29.4%)	-	1(7.7%)
Vision slightly affected	20(16.7%)	5(13.5%)	6(13.8%)	1(25%)	-	4(57.1%)	4(30.8%)
Vision seriously affected	21(19.0%)	4(10.8%)	4(9.3%)	-	4(23.5%)	2(28.5%)	7(53.8%)
Other attacks	43 (35.5%)	14(38.0%)	13(30.2%)	1(25%)	5(29.4%)	3(42.8%)	7(53.8%)
Duration under three months	67(55.3%)	25(67.5%)	28(65.1%)	2(50%)	6(35.2%)	3(42.8%)	3(23.0%)
Duration over three months	32(23.1%)	8(21.6%)	9(20.9%)	1(25%)	4(23.5%)	4(57.1%)	6(46.0%)
Duration over one year	22(18.1%)	4(10.8%)	6(13.9%)	1(25%)	7(41.2%)	-	4(33.0%)

chronicity of patients in Types II and III compared to those in Type I, suggests that there may be some fundamental similarities in the former two groups as well as differences between the non-granulomatous and other types. Consequently in Table XI Types II and III are combined according to the classification advocated by Woods, who considers mutton fat K.P. as being indicative of a granulomatous type of uveitis. When the cases are compared under this new grouping a striking sex difference emerges with a considerable predominance of females compared to males in the granulomatous group. Furthermore it is clear that the prognosis as regards vision is much more serious for females than males as is shown by 40% of the female patients having bilateral involvement while over half of all the cases in the granulomatous group have serious impairment of their vision. Finally, as is to be expected, the cases in this group show a tendency to run a chronic course.

TABLE XI

OCULAR FINDINGS

	All types	Type I		Type II & Type III	
		Non-granulomatous		Granulomatous (Woods)	
		Male (37)	Female (43)	Male (11)	Female (30)
Bilateral	26(21.4%)	4(10.9%)	9(18.9%)	1(9%)	12(40%)
Unilateral	95(78.6%)	33(89.1%)	34(81.1%)	10(91%)	18(60%)
Raised tension	13(10.7%)	5(13.5%)	2(4.6%)	-	6(20%)
Vision slightly affected	20(16.7%)	5(13.5%)	6(13.8%)	5(45.4%)	4(13.3%)
Vision seriously affected	21(19.0%)	4(10.8%)	4(9.3%)	2(18.1%)	11(36.6%)
Other attacks	43(35.5%)	14(38%)	13(30.2%)	4(36.3%)	12(40.3%)
Duration under three months	67(55.3%)	25(67.5%)	28(65.1%)	5(45.4%)	9(30.0%)
Duration over three months	32(23.1%)	8(21.6%)	9(20.9%)	5(45.4%)	10(33.3%)
Duration over one year	22(18.1%)	4(10.8%)	6(13.9%)	-	11(36.6%)

TREATMENT

It is not within the scope of this thesis to discuss in full the treatment of endogenous uveitis, except where the medical care of the patient and the local ocular treatment have some apparently close relationship, for to do more than this would be to trespass on the province of the ophthalmologist. Although a major advance in the symptomatic treatment of uveitis has occurred since the discovery of cortisone, the rational treatment of uveitis is still, unfortunately, only too well summarised by Duke-Elder who said that "treatment is embarked upon with the arrogance of faith and none of the modesty of knowledge".

Systemic Treatment

After the results of the general medical examination had been made known, any condition which required specific treatment was dealt with in the appropriate manner. As may be judged from the section dealing with the medical findings the various forms of therapy, considering the comparatively small number of patients, cover a remarkably wide range of specialities and, as the treatment employed was entirely orthodox, no individual discussion is warranted. Furthermore, no claim may be made that any particular medical treatment produced a rapid resolution of the ocular condition. Even to suggest that this was the case would demand a long period of follow-up and such retrospective reports have in the past proved to be

conflicting (Irons and Brown, Woods and others). It seems probable, however, that the general health of many of the patients must have been improved as a result of the medical treatment they were given and it is consequently reasonable to suppose that this cannot have had any adverse effect on the course of the uveitis. In this respect it is interesting to speculate what effect radiotherapy may have had on those patients with ankylosing spondylitis and whether it has modified the pattern of the recurrent attacks of non-granulomatous uveitis from which the majority suffered. In so far as their general health benefited some remission might be expected though, as radiotherapy is probably only symptomatic and does not strike at the fundamental cause of the spondylitis, which may have a common origin with the uveitis, recurrence of the iritis would not be unexpected. The answer to this will be known only after the lapse of several years.

With respect to focal sepsis and in particular dental sepsis, an interesting point emerges from the treatment of this group. It has been a common clinical observation that interference with a septic focus is often associated with a flare-up of the ocular condition yet in this series this was not observed. This is almost certainly explained by the fact that all the patients received dental treatment while receiving cortisone drops locally and this prevented an ocular exacerbation which might otherwise have been expected to occur in a proportion of the cases.

By reason of the difficulty of evaluating the individual response to the Mantoux test and the very doubtful significance of the varying degrees of cutaneous sensitivity as well as of the very low incidence of tuberculosis in this series, no attempt was made to desensitise any of the patients to increasing concentrations of Old Tuberculin. In various centres, particularly in Europe where a tuberculous aetiology was commonly invoked and particularly if the Mantoux test was strongly positive in high dilutions, desensitisation with tuberculin was embarked upon. This time-consuming technique was never of proven value and sometimes resulted in an ocular flare-up sometimes associated with a particularly florid cutaneous reaction. Though this reaction was never beneficial to the eye it gave some support to the belief that the uvea was particularly sensitive to the products of the tubercle bacillus and consequently fostered the supposition that the uveitis was of tuberculous origin. More recently with the advent of anti-tuberculous chemotherapy, this is given in many clinics to patients who are found to have a high degree of skin sensitivity though the results are so far discouraging and any successes are difficult to assess. Only two patients in this series were given anti-tuberculous chemotherapy and it appeared to have no beneficial effect on their uveitis.

Cortisone Therapy

There can be little doubt that though entirely symptomatic the local administration of cortisone has been the greatest

therapeutic advance in the treatment of the non-granulomatous forms of uveitis. Many of the exacerbations of local inflammation can be well controlled by the local instillation of cortisone drops three or four times a day. More severe reactions may require subconjunctival injections of cortisone every few days but it is very doubtful if resort should be made to systemic cortisone therapy because of the profound disturbances that can result from the incautious use of systemic cortisone and even more of A.C.T.H. Furthermore it has not been definitely established that any greater benefits result from systemic treatment than from local treatment because fortunately, the eye being so readily accessible, locally high concentrations of the steroids can be easily achieved.

In this series, as well as mydriatics, patients were given cortisone drops to instil themselves and in severe cases an injection of cortisone subconjunctivally was also given. Hydrocortisone became available while the investigations on this series of patients were in progress and it was substituted for cortisone as, theoretically at least, it was thought that it might be more active, though up to the time of the completion of the series no superiority was demonstrated. This is supported by the work of Leopold (1954) who has shown that penetration by cortisone into the anterior chamber after subconjunctival injection is much greater than after the injection of a similar quantity of hydrocortisone; the probable explanation of this being that hydrocortisone is only 1/7th. as

soluble as cortisone in body fluids. No patient included in the series was given any adrenocorticotrophic hormone or cortisone systemically, although two patients not included in the series were treated with systemic cortisone and one with A.C.T.H. with no observable success.

The remarkable effect of the suprarenal steroid hormones on the ocular reaction provides an interesting and forceful empirical argument as to the nature of the ocular response and perhaps the aetiology of a large group of cases of uveitis. Although the theories of Selye are not accepted in their entirety by the majority of orthodox medical opinion, there is little disagreement about the part played by the suprarenal cortical hormones in suppressing the inflammatory reaction and modifying the allergic response, as is well demonstrated by the value of cortisone or A.C.T.H. therapy in the non-specific treatment of such allergic conditions as asthma, angioneurotic oedema and other sensitivity reactions. That cortisone is able in many cases to suppress the ocular reaction in uveitis to a great degree does seem to give further support to the theory that many cases of uveitis may be due to the development of an ocular sensitivity to some endogenous or even exogenous source of allergens. In this respect it is also interesting to reflect that protein shock therapy which was practised for so many years with considerable success is now probably explained by the fact that the parenteral injection of milk or typhoid vaccine, and the resulting high febrile response,

stimulates the suprarenal cortex thus liberating endogenous cortisone which in turn exerts a suppressive action on the ocular response. Although it is satisfying that a rational explanation may now be given to a classical pragmatic therapy it does not, unfortunately, do more than indicate that the search for the aetiology of a group of cases of uveitis may be somewhat nearer its goal without as yet by any means achieving it.

SUMMARY AND CONCLUSIONS

The findings in this series differ in several important ways from some larger, though in many ways comparable, series reported from the United States and Europe during the last 25 years. The major differences may be summarised as follows:

1. Although 33.8% of the patients in this series would be classified by Woods as suffering from a "granulomatous" uveitis, only 5.7% at the upper limit could be said on medical grounds to have a "granulomatous" disease.

2. The incidence of focal sepsis in the two groups classified ophthalmologically as "granulomatous" and "non-granulomatous" is virtually identical. Thus, if focal sepsis is an aetiological factor these findings, which conflict with those of Woods, do not support the view that focal sepsis necessarily produces a "non-granulomatous" type of uveitis.

3. Although the general morbidity of the series is high the incidence of diseases such as tuberculosis and venereal disease as well as sarcoidosis, brucellosis and toxoplasmosis is extremely low.

4. 46.2% of the patients in this series would be failed for life assurance on the results of their general medical examination. Although this very high figure includes all age groups it would seem to give support to the view that there is a high morbidity in this group of patients and this particular point has not often been stressed by other workers.

5. The predominance of females over males in the granulomatous group as well as the poorer prognosis for the females in this group give some further support to the generally accepted clinical impression that women have a greater tendency to develop uveitis. This in turn suggests that there may be some endocrine basis for this difference but, until more accurate methods of assessing and investigating deviations from a normal endocrine pattern, nothing of a definite nature can be deduced from these findings.

From any investigation such as this an attempt must be made to draw some conclusions on which a future line of positive action may be based. Some of these may be summarised as follows:

1. Until more definite knowledge is acquired about the aetiology of uveitis the present scheme of investigation and treatment is simple, flexible, and satisfactory. Consequently it would seem advisable that patients should continue to be examined along the broad lines laid down in this thesis.

2. In view of the possible relationship between uveitis and focal sepsis, skin testing techniques modified from those recently described by Woods should be included in future investigations and to these should be added skin testing with cultures prepared from autogenous foci.

3. Depending on the results of the skin testing a positive programme of desensitisation should be carried out.

4. Every effort should be made to improve the general

health of the patients and to maintain their health at as high a level as possible. Thus, without making these unfortunate patients valetudinarians, they should be advised to lead as healthy and restful a life as possible and to protect themselves from any undue stresses and strains in so far as is possible and is consistent with their daily life.

5. As there is as yet no certainty about the aetiology of uveitis nor the best method of treatment that should be adopted, it would be justifiable to start off a long-term controlled trial on this unfortunate group of patients. Obviously there must be no deviation from the line of treatment that is already accepted as standard and this of course now includes the use of steroid hormones whenever they are thought necessary. Skin testing and desensitisation techniques are, however, complicated and time-consuming and their value is by no means established, and it would thus seem highly desirable to put them on trial under controlled conditions. To do this it seems likely that the best method would be, in so far as is possible, for patients to be paired as regards age, sex and ophthalmological findings. One patient could then be given the standard form of treatment and the other could undergo a full course of desensitisation. As the value of this has not yet been established no ethical problem would be involved and the patients could then be carefully followed up over a period of years. In order to reduce the number of patients in this trial to a minimum consistent with achieving results of statis-

tical significance, the results should be analysed sequentially as described by Bross (1952). In this way it is hoped that though the investigation would probably have to be continued for a number of years, some positive evidence as to the best form of treatment might result and this in turn might shed some further light on the aetiology of the condition.

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APPENDIX A

CONTROL SERIES OF PATIENTS

Both from ethical as well as practical considerations it is often difficult to justify the inclusion of a large series of patients merely for "control" purposes. Nevertheless it is at times highly desirable to have information about such a group. In this series where no controls were required in order to assess therapy the problem though less complex still presented considerable difficulties.

After the investigation had been under way for some time it became clear that considerable importance might be attached to radiological evidence with particular reference to dental sepsis. While no information was available about the incidence of positive radiological evidence of dental sepsis in a random sample of the population it was decided that some attempt should be made to acquire this. Although the following method adopted was not the one of choice it was hoped that it would be the least inconvenient for the patients as well as the least disruptive of hospital routine.

The patients, who were from wards under the charge of Professor Scott, had been admitted because of some non-inflammatory eye condition, were referred to the radiological department some time during their stay in hospital. They were radiographed according to the same plan as those patients suffering from uveitis and their films were scrutinised by the

same radiologist who reported on the films of those patients with uveitis. The radiologist was at no time aware of the underlying ocular pathology of the patient on whom he was reporting. It was decided that only 50 patients should be included in the control group and as they were chosen by, and seen by the House Officer of the Ophthalmological Ward no selecting bias was likely to occur. By reason of its limited number, however, the group was not strictly comparable to the uveitis group as regards age and sex. The predominance of males in particular was accounted for by the relatively higher proportion of apparently healthy males admitted to hospital because of eye injuries. Unfortunately none of the patients could be referred for subsequent dental investigation or treatment so little further can be deduced from the figures in Table XII.

The high incidence of radiological evidence of dental sepsis in an apparently healthy group of patients is, however, very striking and this figure alone seems to have justified the necessary precaution of acquiring information about this group of patients before drawing sweeping conclusions about those suffering from uveitis.

TABLE XII

Control Group of 50 Patients - Radiological Findings

	Dental Sepsis	Infected Sinuses	Lumbar and S.I. Joints	Chest
Males	29.4%	29.4%	-	-
Females	43.7%	31.2%	-	-
Total Incidence	32 %	30 %		

APPENDIX B

BACTERIOLOGICAL FINDINGS

Summary and Conclusions

1. Streptococci were found almost exclusively in cultures from the root canals of infected teeth extracted from patients suffering from uveitis.

2. The differentiation of these streptococci has been investigated and discussed.

3. The findings lend support to the view that where an endogenous uveitis is associated with a focus of infection the organisms involved are streptococci of low grade pathogenicity.